REMARKS

In the Final Action dated July 16, 2003, claims 7-15 and 17-18 are pending. Claims 7, 9-13 and 17-18 are withdrawn from consideration. Claims 8 and 14-15 are rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled.

This Response addresses each of the Examiner's rejections. Applicants therefore respectfully submit that the present application is in condition for allowance or at least in better condition for appeal. Favorable consideration of all pending claims is therefore respectfully requested.

Claims 7, 9-13 and 17-18 are withdrawn from consideration. Applicants have canceled claims 7, 9-13 and 17-18 without prejudice by way of the instant amendment.

Claims 8 and 14-15 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enabling support.

The Examiner admits that the specification is enabling for a method of increasing cartilage deposition in a mammal suffering from Sox-9 deficiency that leads to a breakage, degeneration, depletion or damage of bone or cartilage forming cells in the mammal; the method comprising administering directly to the cells, a DNA molecule comprising a promoter operably linked to the nucleotide sequence as set forth in SEQ ID NO: 20, or a nucleotide sequence coding for a SOC-9 polypeptide, wherein said SOC-9 polypeptide comprises the amino acid sequence as set forth in SEQ ID NO: 21.

However, the Examiner contends that the specification does not reasonably provide enablement for the claimed methods which, according to the Examiner, encompass treatment by administration of any SOX-9 DNA, regardless of the presence of an operably linked promoter or expression cassette, to any animal (including reptiles, birds, amphibians,

mammals), any disease associated with a breakage, degeneration, depletion or damage of bone or cartilage, wherein the disease is not necessarily caused by SOX-9 deficiency or its loss of function. Specifically, the Examiner contends that neither the application nor the incorporated references demonstrate any therapeutic effect in an animal having a bone or cartilage disease other than a mammal. The Examiner states that neither the application nor the claims recite the subjects or the bone diseases that are affected by the claimed treatments.

Applicants submit that the bone disorder that is treated by the claimed method is already recited in the claims, i.e., breakage, degeneration, depletion or damage of bone or cartilage. In addition, in an effort to favorably advance the prosecution of the present application, Applicants have amended independent claim 8 to define the animal treated to be a mammal. Support for such amendment is found in the specification, e.g., at page 38, line 6.

With respect to the cause of the disorders recited in the claims, Applicants submit that there may be a variety of direct and indirect causes that lead to these disorders. A unique recognition of the present invention is that the SOX-9 protein is important to bone and cartilage formation, and that SOX-9 can be used to promote bone and cartilage differentiation and growth thereby ameliorating the conditions involving bone and cartilage depletion or damage. There is no requirement that the disorder is directly caused by a deficiency in the expression or function of the SOX-9 protein in order for the claimed method to be effective.

Applicants further submit that in light of the specification, those skilled in the art would understand that a principal feature of the claimed invention resides in the introduction of the SOX-9 DNA into the mammal for regenerating bone or cartilage and that there are a variety of means to achieve the expression of the SOX-9 protein from the administered DNA molecule, e.g., by linking a promoter to the SOX-9 nucleotide sequence. Thus, it is not necessary to

recite in the claims that the SOX-9 nucleotide sequence is linked to a promoter. Applicants have, however, amended claim 8 to recite that the DNA molecule is administered such that the encoded SOX-9 protein is expressed, leading to regeneration of bone or cartilage.

The Examiner also contends that any gene transfer or gene therapy protocol involves issues such as the amount of DNA constructs to be administered to be therapeutically effective, the route and time course of administration, the sites of administration, successful uptake of the claimed DNA at the target site, and expression of the DNA at the target site in sufficient amounts. The Examiner contends that neither the specification nor the incorporated references provide sufficient guidance as to the foregoing parameters.

In this regard, Applicants respectfully submit that suitable routes of administration are described in the specification. Specifically, the Examiner's attention is respectfully directed to page 11, line 1 to page 12, line 8 of the specification, where it is described that administration can be achieved by injection (including local injection where effects are restricted to specific bones, cartilage or regions of bones or cartilage), implantation, instillation or other means of a SOX-9 nucleic acid molecule, and that the SOX-9 nucleic acid molecule can be administered alone, or in combination with liposomes, viral capsids or nanoparticles, or any other mediator of delivery.

Applicants further respectfully submit that teachings regarding various aspects of gene therapy, such as available gene delivery systems (viral or non-viral based), choices of viral vectors, and targeted expression, are readily available to those skilled in the art. As examples of such teachings and as evidence of the level of skill of those in the art, Applicants provide herewith review articles published before the priority date of the present application (May 29, 1997) by Smith et al. (*Gene Therapy* 3:190-200, 1996; **Exhibit 1**), Rolland

(*Targeting of Drugs 5: Strategies for Oligonucleotide and Gene Delivery in* Therap pp: 79-95, 1996; **Exhibit 2**), Becker et al. (*J Mol Med 73*:103-105, 1995; **Exhibit 3**), and Gunzburg et al. (*Cytokines and Molecular Therapy 2*:177-184, 1996; **Exhibit 4**), which discuss in great detail gene delivery systems (viral or non-viral based), choices of viral vectors, targeted expression, and other related issues involved in gene therapy. Based on these references, it is apparent that gene therapy had evidenced success by the time the priority application was filed on May 29, 1997.

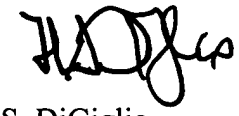
With respect to the effective dosage of the nucleic acid molecule to be administered, such dosage can be determined by those skilled in the art by performing routine experimentation and optimization. Applicants respectfully submit that some experimentation is permissible. In re Wands, 858 F.2d 731, 736-737, 8 U.S.P.Q. 1400, 1404 (Fed Cir. 1988). Necessary experimentation is not determinative of the question of enablement; only undue experimentation is fatal under the provisions of 35 U.S.C. §112, first paragraph. Id.

In view of the foregoing, it is respectfully submitted that the claimed methods of regeneration of bone or cartilage using a Sox-9 DNA molecule is fully supported by the specification. Those skilled in the art would be able to practice the claimed methods without undue experimentation. Thus, the rejection under 35 U.S.C. §112, first paragraph, is overcome. Withdrawal of the rejection is respectfully requested.

Furthermore, Applicants have added claim 19 to more specifically delineate a preferred embodiment of the present invention, i.e., where the DNA molecule is administered locally to the region where said breakage, degeneration, depletion or damage of bone or cartilage occurs in the mammal. Support for claim 19 is found throughout the specification, e.g., at page 11, lines 1-9. No new matter is added.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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Encls: Exhibits 1-4